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Effect of parental age on treatment response in adolescents with schizophrenia☆,☆☆

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ABSTRACT

Background: Advanced paternal age (APA) is associated with increased risk for schizophrenia, but its effect on treatment response has not been longitudinally studied.
Methods: Association of parental ages at the time of the child's birth with age of onset, initial symptom severity and treatment response (to placebo and three different weight-based doses of paliperidone ER) in adolescents with schizophrenia was assessed in a post-hoc analysis using data from a 6-week double-blind study, the primary results of which are published (NCT00518323).
Results: The mean (SD) paternal age was 29.2 (6.2) years, range (16–50) and maternal age was 26.8 (5.7) years, range (17–42) at childbirth for the 201 adolescents (ages 12–17 years) included in the analysis. While parental ages were uncorrelated with age of onset or initial symptom severity, both maternal and paternal ages showed significant effects on treatment response ($p < 0.03$) of all paliperidone ER arms versus placebo. Paternal age was significantly correlated to improvement in positive symptoms and maternal age significantly related to negative symptoms, although only paternal age remained significantly associated with the treatment response in analyses that included both parents' ages.
Conclusions: APA was associated with greater treatment response to both paliperidone ER and placebo, but not to age of onset or initial symptom severity in adolescents with schizophrenia. The results support the contention that APA-related schizophrenia has distinct underpinnings from other cases. Further studies are required to explore the role of genetic and environmental factors, and their interactions, in treatment response in this complex disorder.

1. Introduction

An association between advanced paternal age (APA) and the risk for schizophrenia in offspring is well-described (Malaspina et al., 2001; Matheson et al., 2011). While relationships between parental ages and illness features have sometimes been ascribed to the social or other environmental consequences of older parents (Torrey et al., 2009), the emerging literature supports molecular-level drivers for these effects. Following puberty, there are ongoing cell replication cycles in the paternal germ line that provide opportunities for de novo mutations through copy errors of the genome, with APA being the main source of de novo mutations in the human population (Hehir-Kwa et al., 2011; Goriely and Wilkie, 2012). Moreover, specific de novo mutations were recently found in association with schizophrenia in the Icelandic genetic cohort (Kong et al., 2012). There is reason to hypothesize that the mutations producing schizophrenia in association with paternal aging, which is linearly associated with the risk for disease, are acting in influence of particular molecular pathways (Goriely et al., 2013). Moreover, a recent report of 50 de novo mutations for schizophrenia found that these genes acted in a network that influenced the neurodevelopment of the dorsolateral and ventrolateral prefrontal cortex during fetal development, suggesting that the diverse mutations influenced a particular pathophysiology that was relevant to schizophrenia (Gulsuner et al., 2013).

There is growing evidence that particular etiologies differentially influence disease characteristics within the schizophrenia syndrome (Malaspina et al., 2002), and APA is an appealing candidate to explore the impact of etiological differences on treatment response in the

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disease. In an earlier cross-sectional study, wherein treatment response was estimated, sporadic cases with older fathers had significantly more severe positive symptoms when they were off antipsychotic medications, but had similar symptoms to other patients during optimal treatment (Rosenfield et al., 2010). In the current study we had the opportunity to perform a post-hoc examination of the effect of paternal age on treatment response using data from a 6-week, placebo-controlled, international trial (Singh et al., 2011). The study had demonstrated that paliperidone extended-release (ER) dosed at 3–12 mg/day was efficacious in treating schizophrenia in adolescents (ages 12–17). In the current analysis, we studied the effect of parental age on age of onset, symptom severity, and treatment response in adolescents with schizophrenia.

2. Methods

2.1. Study population

Detailed inclusion criteria are provided in the primary publication (Singh et al., 2011). The major inclusion criteria were: Adolescents of either sex, between 12 and 17 years of age (inclusive), weighing at least 29 kg, with a baseline Positive and Negative Syndrome Scale (PANSS) total score of 60 to 120 (inclusive), patients with a Kiddie-Schedule for Affective Disorders and Schizophrenia-Present and Lifetime Version (KSADS-PL) version 1.0 (Kaufman et al., 1997) confirmed diagnosis of schizophrenia (Diagnostic and Statistical Manual, 4th edition [DSM-IV] criteria) for at least one year before screening, and a history of at least one adequate antipsychotic treatment. The main exclusion criteria included a DSM-IV diagnosis other than schizophrenia, and substance dependence (DSM-IV criteria) in the three months preceding screening.

The study protocol was approved by an Independent Ethics Committee or Institutional Review Board at each study site; ethical standards were followed in accordance with the Declaration of Helsinki and consistent with ICH Good Clinical Practices, and local regulatory requirements. A Data Safety Monitoring Board was established to monitor the safety of patients in the clinical trial and ensuring the integrity of the study. All enrolled patients provided written assent, and their parents or legal guardians gave a written informed consent to permit the patient's participation.

2.2. Study design

The study consisted of an up to 21-day screening and washout phase, and a 6-week double-blind treatment phase. Patients were followed up 1 week after study completion for safety evaluations if they did not enter a long-term open-label extension study. During the double-blind treatment phase, patients were randomly assigned (1:1:1:1) to receive either placebo or one of three weight-based, fixed doses of paliperidone ER, once-daily (patient weight at baseline: 29 to <51 kg: 1.5 mg [Low], 3 mg [Medium], or 6 mg [High]; ≥51 kg: 1.5 mg [Low], 6 mg [Medium], or 12 mg [High]) (Singh et al., 2011).

2.3. Assessments

The primary efficacy variable of the study was the change in the PANSS total score from baseline to double-blind endpoint (Singh et al., 2011). In this post-hoc analysis, we examined the following questions: Is parental age related to 1. the age of onset of schizophrenia, 2. initial disease severity at entry into the trial, and 3. treatment response?; Is the relationship of parental age to schizophrenia onset different by sex of child? Are there any predictors of response such as parental age, age of child at diagnosis, sex, severity of disease at trial entry, and previous hospitalizations? We also considered change from baseline in PANSS total score, PANSS subscales (positive, negative, general) and Marder factors (positive symptoms, negative symptoms, disorganized thoughts, uncontrolled hostility/excitement, anxiety/depression). The age of the adolescent patients and their parents was recorded at enrollment and used to calculate the parents' age (in years) at the time of their adolescent's birth.

2.4. Statistical methods

Data from the intent-to-treat (ITT) analysis set, which included all enrolled patients who received at least one dose of study medication and had both baseline and at least one post-baseline assessment, was used for this post-hoc analysis. Correlations between parental ages with age of onset of schizophrenia in child, symptom severity, and response to treatment (a dichotomous category defined as a 20% or more improvement in PANSS total score from baseline ratings) were calculated. For correlation of parental age with response, the groups were categorized as placebo, 1.5 mg paliperidone group ("Pali Low"; shown to be an ineffective dose) and paliperidone ER combined effective doses 3–12 mg ("Pali Med/High"). Correlation of parental age with percent change from baseline in PANSS total score, change from baseline in PANSS total score, PANSS subscales, and Marder factor scores were also performed. The correlations were repeated within each sex subgroup.

Logistic regression models were used to identify factors associated with treatment response. The following variables were included: paternal age, maternal age, sex, age at diagnosis, baseline PANSS total score, prior hospitalizations and treatment group. Maternal age, transformed into "centered" maternal age (defined as: maternal age-mean maternal age) was used to avoid collinearity as maternal age is highly correlated with paternal age. The logistic regression models were also computed using the difference between paternal age and maternal age (instead of either paternal age or centered maternal age), and sex-by-paternal age interaction. Similar analyses were carried out using analysis of covariance (ANCOVA) models on the change from baseline in PANSS total score with baseline value as covariate and accounting for the same variables used in the logistic regression model.

3. Results

Of 228 patients screened, 201 randomly received one of the 4 treatment doses (ITT set: N = 200) and 138 (69%) completed the study. Baseline and demographic characteristics were generally comparable across treatment groups; more boys than girls were in the paliperidone ER treatment groups and more girls in the placebo group (Table 1). 71% of patients had a diagnosis of paranoid schizophrenia. Mean (SD) paternal age was 29.2 (6.2) years, range 16–50; and maternal age was 26.8 (5.7) years, range 17–42. More than half (53.5%) of the patients were ≤13 years of age at diagnosis.

3.1. Effect of parental age on patient's age at diagnosis of schizophrenia or initial severity of disease at study entry

Parental ages at birth of their child were not significantly correlated to the age at diagnosis of schizophrenia in these adolescents (mother's age: $r = 0.066$, $p = 0.392$; father's age: $r = 0.083$, $p = 0.295$). Initial severity was assessed using screening visit PANSS total score, baseline PANSS total score, baseline Clinical Global Impression-Severity (CGI-S) scale, and the number of prior hospitalizations for psychosis. There was no significant effect of maternal age on screening visit PANSS total score ($r = -0.05$, $p = 0.503$), baseline PANSS total score ($r = -0.06$, $p = 0.471$), baseline CGI-S ($r = 0.04$, $p = 0.626$), and the number of prior hospitalizations for psychosis ($r = 0.01$, $p = 0.930$). Similar results were obtained for paternal age and screening visit PANSS total score ($r = -0.05$, $p = 0.550$), baseline PANSS total score ($r = -0.04$, $p = 0.633$), baseline CGI-S ($r = 0.06$, $p = 0.429$), and the number of prior hospitalizations for psychosis ($r = -0.01$, $p = 0.911$).

Mean (SD) age of schizophrenia onset was: boys, 13.1 (2.5) years (range: 3–16); girls, 12.7 (2.8) years (range 4–16). There was no significant effect of maternal or paternal age at birth of the child on the age of

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Table 1
Demographic and baseline characteristics of patients (intent-to-treat analysis set).

	Placebo (N = 51)	Paliperidone ER		
		Low-treatment group (N = 54)	Medium-treatment group (N = 48)	High-treatment group (N = 47)
Age (years), mean (SD)	16 (1.4)	15 (1.5)	15 (1.6)	16 (1.6)
Sex, n (%)				
Boys	23 (45)	30 (56)	31 (65)	33 (70)
Girls	28 (55)	24 (44)	17 (35)	14 (30)
Race, n (%)				
White	35 (69)	35 (65)	34 (71)	32 (68)
Black	4 (8)	5 (9)	3 (6)	5 (11)
Asian[a]	12 (24)	14 (26)	11 (23)	10 (21)
Weight (kg), mean (SD)	60 (16.5)	60 (16.1)	58 (14.6)	62 (16.1)
Body weight category, n (%)				
<51 kg	14 (27)	19 (35)	16 (33)	13 (28)
≥51 kg	37 (73)	35 (65)	32 (67)	34 (72)
BMI (kg/m^2), mean (SD)	22 (5.6)	22 (4.9)	21 (4.0)	22 (4.3)
Duration of illness (years), mean (SD)	2.3 (1.7)	2.6 (2.1)	2.2 (1.4)	2.7 (2.3)
Age at diagnosis of schizophrenia (years), mean (SD)	13.4 (2.4)	12.5 (2.9)	13 (1.9)	12.8 (3.2)
Baseline PANSS total score				
Mean (SD)	90.6 (12.13)	91.6 (12.54)	90.6 (14.01)	91.5 (13.86)
Baseline CGI-S (n, %)				
Very Mild	0	1 (2)	0	0
Mild	3 (6)	3 (6)	3 (6)	2 (4)
Moderate	27 (53)	28 (52)	19 (40)	26 (55)
Marked	19 (37)	19 (35)	21 (44)	14 (30)
Severe	2 (4)	3 (6)	5 (10)	5 (11)
Prior psychotropic therapy, n (%)				
Total number of patients with prior psychotropic therapy	48 (94)	47 (87)	44 (92)	40 (85)
Atypical antipsychotics	34 (67)	35 (65)	32 (67)	27 (57)
Typical antipsychotics	21 (41)	18 (33)	22 (46)	19 (40)
Prior hospitalizations (n, %)				
None	18 (35)	26 (48)	19 (40)	18 (38)
Once	10 (20)	14 (26)	17 (35)	15 (32)
Twice	13 (25)	6 (11)	6 (13)	6 (13)
Three times	4 (8)	2 (4)	1 (2)	4 (9)
Four times or more	6 (12)	6 (11)	5 (10)	4 (9)

[a] Asian Indian and Asian Other (Taiwanese, Vietnamese and Chinese–Vietnamese) categories grouped as Asian; BMI = body mass index; CGI-S = clinical Global Impression-Severity scale; PANSS = Positive and Negative Syndrome Scale; SD = standard deviation.

onset of schizophrenia by sex in this patient sample. Among adolescent girls and boys, age of onset of schizophrenia was not significantly correlated with parental age; maternal age, girls — n = 67, r = 0.13, p = 0.297, boys — n = 102, r = 0.02, p = 0.804; paternal age, girls — n = 64, r = 0.03, p = 0.814, boys — n = 96, r = 0.13, p = 0.201.

3.2. Effect of parental age on change from baseline PANSS total score and subscales at endpoint

Both maternal (n = 169, r = −0.18, p = 0.02) and paternal (n = 160, r = −0.17, p = 0.03) age correlated with percent change from baseline across all groups (i.e., placebo and all paliperidone ER arms combined) (Fig. 1).

When parental ages were examined with respect to individual treatment groups by response status, the correlation persisted (although smaller sample sizes reduced the significance), suggesting that in both the active- and placebo-treatment groups, adolescents born to older parents had an improved response compared with those born to younger parents (Fig. 2A,B).

Correlations ranging from −0.07 to −0.22 were observed between parental age and change in PANSS total score, the three PANSS subscales and the five PANSS factors (Marder et al., 1997). Similar results were obtained when the correlations were examined separately among adolescent boys and girls (Table 2A). For the PANSS subscales, paternal age was significantly correlated with change in the negative subscale, particularly for adolescent boys, whereas maternal age was significantly correlated with change in the positive subscale symptom score. Marder factor scores showed significant paternal and maternal age relationships to positive symptom change but not to other factors (Tables 2A, 2B).

3.3. Effect of parental age on treatment response

Parental ages were consistently higher for responders (≥20% reduction in PANSS total scores) versus non-responders. Compared with non-

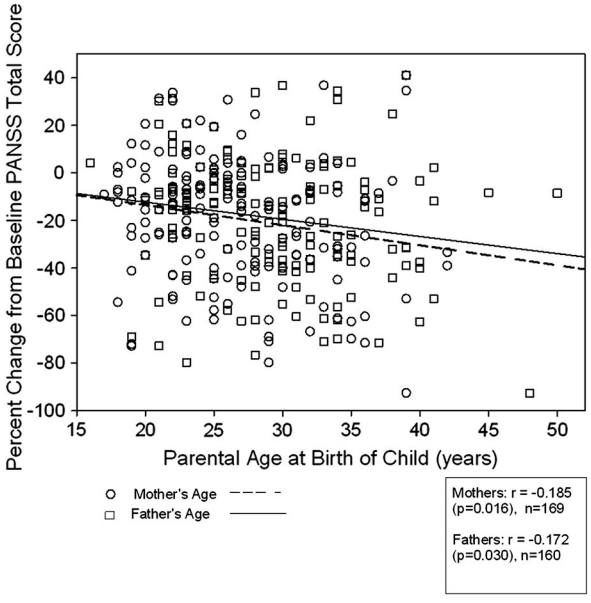

Fig. 1. Percent change from baseline in PANSS total score at endpoint vs parental age at birth of child (intent-to-treat analysis set).

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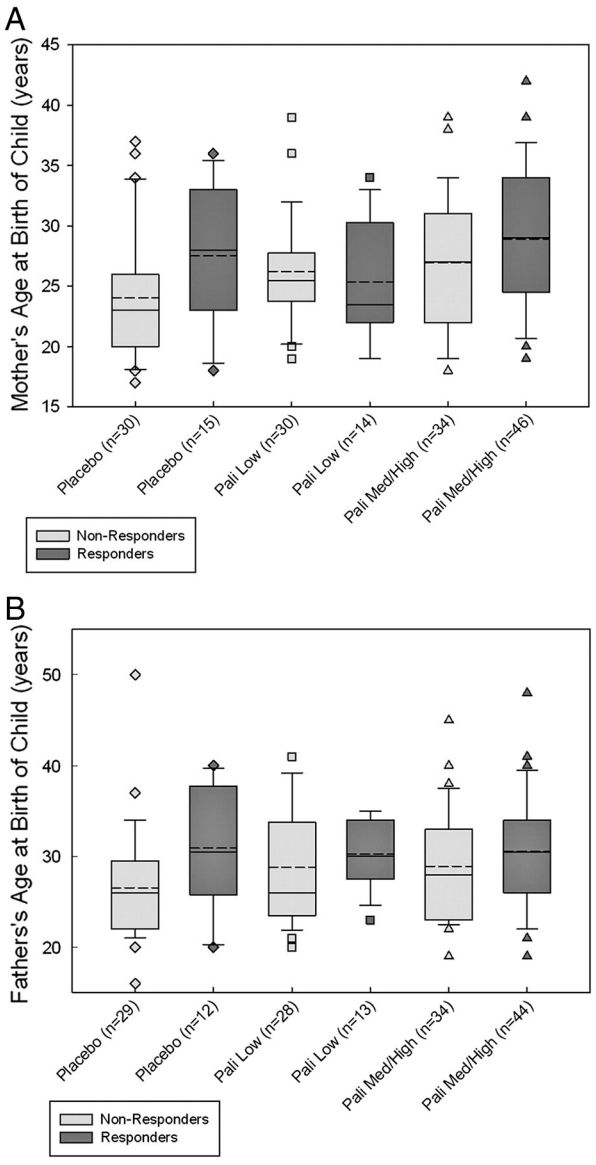

Fig. 2. Effect of parental age on response status in individual treatment groups (intent-to-treat analysis set). 2A. Maternal age; 2B. Paternal age. In both the active- and placebo-treatment groups, improved response was observed in adolescents born to older parents than those born to younger parents.

responders, the paternal age of responders was on average 4.4 years greater in the placebo group and 1.6 years greater in the Pali Med/High group. Similarly, maternal age of responders was on average 3.5 years greater in the placebo group and 1.9 years greater in the Pali Med/High group.

Univariate significant predictors of response were Pali Med/High group ($p = 0.002$), paternal age ($p = 0.016$), and maternal age ($p = 0.015$), Table 3. However, the difference between paternal age and maternal age was not a significant predictor of response ($p = 0.752$). When all variables were included in the logistic model, the only significant predictor of response was Pali Med/High group. There was no significant correlation between paternal age and sex ($p = 0.921$).

4. Discussion

The results of this study show that paternal age influences treatment response to positive symptoms in adolescents with schizophrenia. This analysis was conducted post-hoc in data from a multinational, double-blind, placebo-controlled efficacy and safety study of an atypical antipsychotic. These findings offer intriguing support for the hypothesis that parental age influences treatment response in schizophrenia. Notably, these patients were adolescents with early-onset schizophrenia. Most were diagnosed by age ≤13 years, constituting a sample with early age of onset even in comparison to other adolescent schizophrenia studies (Mattai et al., 2010). This analysis demonstrated a significant, albeit modest, correlation of paternal age with treatment response in adolescents with schizophrenia, but not with the age of onset or initial symptom severity in the offspring.

While the average paternal age (29.2 years) at the time of birth of these adolescents with schizophrenia does not appear noteworthy, the paternal age range was broad, spanning16-50 years. The risk for schizophrenia in offspring increases linearly with paternal age (Malaspina et al., 2001; Byrne et al., 2003; Buizer-Voskamp et al., 2011; Hubert et al., 2011; Miller et al., 2011). Although the risk to fathers who are in their thirties is only slightly increased for schizophrenia, they bear the largest proportion of offspring, which translates into very large population-wide effects because a vastly larger proportion of these men produce children.

In this study of early onset adolescents, there was no sex difference in age of onset unlike what is seen on an average in adult samples, where females have a 5-year later onset than males (Hafner et al., 1989; Hafner and an der Heiden, 1997). Consistent with the current results, a large population birth cohort study also found no sex differences in the onset of childhood schizophrenia. A study comparing the age of onset in males and females judged to have 'paternal age related schizophrenia' also found no sex differences in the ages of onset and also

Table 2A
Correlation of parental age with change in PANSS total score and subscale scores.

	All patients		Boys		Girls	
	Maternal age (n = 169)	Paternal age (n = 160)	Maternal age (n = 102)	Paternal age (n = 96)	Maternal age (n = 67)	Paternal age (n = 64)
PANSS total score	−0.174*	−0.165*	−0.154	−0.175	−0.196	−0.145
PANSS subscales						
Positive	−0.181*	−0.151	−0.184	−0.131	−0.177	−0.166
Negative	−0.131	−0.175*	−0.174	−0.227*	−0.060	−0.092
General psychopathology	−0.151	−0.131	−0.070	−0.122	−0.243*	−0.130
Marder factors						
Positive symptoms	−0.215*	−0.181*	−0.177	−0.160	−0.260*	−0.194
Negative symptoms	−0.100	−0.136	−0.111	−0.172	−0.080	−0.074
Disorganized thoughts	−0.082	−0.074	−0.054	−0.114	−0.114	−0.028
Uncontrolled hostility/excitement	−0.143	−0.122	−0.175	−0.141	−0.094	−0.088
Anxiety/depression	−0.113	−0.122	−0.036	−0.070	−0.232	−0.194

Note: Sample based on those who had at least one parental age recorded. The baseline characteristics of this group were not different from the total number of patients included in Table 1.
PANSS = Positive and Negative Syndrome Scale.
* $p < 0.05$.

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Table 2B
Correlation of parental age with change in PANSS total score and subscale scores by treatment group.

	Placebo		Low dose		Med/high dose	
	Maternal age (n = 45)	Paternal age (n = 41)	Maternal age (n = 44)	Paternal age (n = 41)	Maternal age (n = 80)	Paternal age (n = 78)
PANSS total score	−0.240	−0.293	0.045	−0.069	−0.137	−0.072
PANSS subscales						
Positive	−0.148	−0.154	0.030	−0.119	−0.182	−0.108
Negative	−0.283	−0.352	0.068	−0.027	−0.035	−0.052
General psychopathology	−0.236	−0.292	0.033	−0.038	−0.114	−0.038
Marder factors						
Positive symptoms	−0.234	−0.259	−0.011	−0.148	−0.229	−0.111
Negative symptoms	−0.284	−0.319	0.152	0.093	−0.029	−0.061
Disorganized thoughts	−0.156	−0.241	−0.011	−0.069	0.044	0.119
Uncontrolled hostility/excitement	−0.106	−0.132	−0.052	−0.097	−0.127	−0.066
Anxiety/depression	−0.165	−0.163	0.185	0.033	−0.121	−0.126

PANSS = Positive and Negative Syndrome Scale.

found more severe illness in females than males with older fathers (Rosenfield et al., 2010).

The beneficial effect of paternal age on treatment response is similar in this study and that of Rosenfield et al. (2010). The present longitudinal placebo-controlled treatment study is unique in several ways; rather than stratify cases based on judgments about etiology, paternal age was evaluated as a treatment response modifier in all patients. This study demonstrates that paternal age is a viable and valuable concept in early-onset forms of the disease, which had not been previously explored.

The heterogeneity of treatment response in schizophrenia has long been a focus of investigation and is a major research priority. Some genetic (Lee et al., 2011b) and imaging data (Szeszko et al., 2010) reports have shown promising results for prediction of response to a specific agent or class of agents. The present study is the first to provide evidence of differential treatment response correlating with an etiologic factor in an early-onset population: in a multinational sample, adolescent patients born to older parents had greater treatment response, irrespective of the treatment (paliperidone ER or placebo). The correlations overall were small, but significant, and have the potential to impact treatment effects when applied to larger populations and longer treatment durations.

Subscale analyses indicate the possibility of greater paternal (but not maternal) age effects on negative symptom treatment response, which are less responsive to treatment and therefore, of particular interest. Paternal age is also significantly related to the risk for autism (Lundstrom et al., 2010; Hultman et al., 2011) and autistic symptoms (e.g. poor socialization), similar to negative symptoms in schizophrenia (Van den Oord et al., 2006). A comparable model may explain the independent effects of maternal age effects, as well-demonstrated in autism (Sandin et al., 2012). Results suggest that maternal age may be associated with positive symptom response, which deserves further study. Although maternal age has not been independently linked to the risk for schizophrenia in epidemiological studies, maternal age may influence illness features and response within the disease. Both paternal and maternal age showed significant effects on the positive symptom scores, but not on scores of the other Marder factors including the negative symptom factor. The effect of parental age on symptom domains needs to be confirmed in future studies of adolescent schizophrenia.

Notably, treatment responders were more likely to have older parents than nonresponders. The improved treatment response may arise from the paternal age related enhancement of genes in treatment responsive pathways that predict a better response to both antipsychotics and to placebo. The data presented here add to earlier reports (Malaspina et al., 2000, 2001), which hypothesize that advanced paternal age contributes to a specific schizophrenia subtype in the offspring that is more treatment responsive. We have repeatedly shown higher verbal IQ than performance IQ in association with later paternal age in adult clinical cases (Malaspina et al., 2002; Lee et al., 2011a) and in healthy adolescents (Malaspina et al., 2005). Similarly, we found lower verbal intelligence in familial schizophrenia (Wolitzky et al., 2006) and decreased neural blood flow in left-sided language areas in familial, but not in sporadic cases associated with later paternal age in schizophrenia (Malaspina et al., 2004).

This was a post-hoc analysis, designed after study completion. There may be limitations pertaining to generalizability as patient selection was based on specific criteria, rather than randomization from a representative sample of patients with early onset schizophrenia. Aspects of these findings may be specific to early onset patients and may not apply to those with onset in adulthood.

Despite different underpinnings of the schizophrenia syndrome, it remains a condition that is typically diagnosed in late adolescence or early

Table 3
Odds ratios (and 95% CI) from logistic regression analysis assessing the effect of different factors on treatment response in adolescents with schizophrenia.

	Non-adjusted			Adjusted		
Variable	OR	95% CI	p-Value	OR	95% CI	p-Value
Treatment						
Low vs PB	1.273	0.572–2.829	0.427	1.091	0.387–3.074	0.202
Medium/High vs PB	2.750	1.351–5.596	0.002	3.561	1.431–8.861	0.001
Paternal age	1.067	1.012–1.125	0.016	1.029	0.953–1.112	0.466
Centered maternal age	1.072	1.014–1.134	0.015	1.029	0.945–1.121	0.510
Gender	0.967	0.550–1.699	0.907	0.565	0.269–1.187	0.132
Diagnosis age	1.098	0.983–1.226	0.098	1.092	0.957–1.247	0.193
Baseline PANSS	0.985	0.964–1.006	0.169	0.994	0.965–1.023	0.666
Prior hospitalizations	0.956	0.768–1.190	0.688	1.046	0.802–1.366	0.739
Paternal age * gender interaction						0.921

CI = Confidence interval; OR = odds ratio; PANSS = Positive and Negative Syndrome Scale; PB = placebo.

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adulthood, when psychosis emerges. The lack of differences in age of onset or other demographic features at study baseline is not unexpected, given the ascertainment platforms and inclusion criteria for a clinical trial. Rather, the associations with outcome are even more robust.

The potential role of psychosocial environment associated with growing up with a relatively "older" father, such as increased occurrence of adverse life events or differences in parenting style, may contribute to the results. Conversely, the role of psychosocial factors is not supported by data showing a lack of any effects of fathers' age in adopted offspring (Ek et al., 2012).

Adolescents with schizophrenia born to older fathers had greater treatment response, in both active treatment and placebo groups, suggesting that older paternal age-related schizophrenia has distinct underpinnings. Further studies are warranted to replicate these results and explore the role and interactions of genetic and environmental factors in treatment response in this complex disorder.

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Contributors

All authors meet ICMJE criteria and all those who fulfilled those criteria are listed as authors. All authors had access to the study data, contributed to the analysis and interpretation of the data, were involved in the manuscript from its conception, critically reviewed each draft, and provided comments and guidance on its direction, and made the final decision about where to publish these data. All authors contributed to the study design, analysis and interpretation of data. Dr. Opler was an expert for the study. Dr. Nuamah also conducted the statistical analyses and provided the figures.

Conflict of interest

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